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| 10/519,342 | 09/21/2005 | Dean Y Li | UUTH-PO1-010 | 2504 |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

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|------------------------------|--------------------------------------|----------------------------------|
| Office Action Summary | Application No. 10/519,342 | Applicant(s) LI ET AL. |
| | Examiner David S. Romeo | Art Unit 1647 |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 28 January 2008.
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 1-22 is/are pending in the application.
 4a) Of the above claim(s) 1-6 and 13-18 is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 7-12 and 19-22 is/are rejected.
 7) Claim(s) _____ is/are objected to.
 8) Claim(s) 1-22 are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on 21 December 2004 is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) Notice of References Cited (PTO-892)
 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
 3) Information Disclosure Statement(s) (PTO/SB/08)
 Paper No(s)/Mail Date 0205.

4) Interview Summary (PTO-413)
 Paper No(s)/Mail Date. _____.
 5) Notice of Informal Patent Application
 6) Other: _____

DETAILED ACTION

Claims 1–22 are pending.

Applicant's election of group V, claims 7–12 and 19–22 in the reply filed on 01/28/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed 5 errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1–6 and 13–18 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking 10 claim. Election was made **without** traverse in the reply filed on 01/28/2008.

10 ***Specification***

Figure 6 is presented on separate panels, i.e., "A" and "B". However, the brief 15 description of the drawings refers only to Figure 6. This is an error in the specification which must be corrected. For Example, if the drawings show Figures 1A, 1B, and 1C, and the brief description of the drawings refers only to Figure 1, this is an error in the specification which must be corrected. See MPEP § 601.01(g). The Brief Description of the Drawings and the rest of the specification must be amended to refer to Figures 6A and 6B.

Correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the 20 basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 19–22 are rejected under 35 U.S.C. 102(b) as being anticipated by Geng (FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A8) in view of Huminiecki (Genomics. 2002 Apr;79(4):547-52).

A 35 U.S.C. 102 rejection over multiple references has been held to be proper when the

5 extra references are cited to:

- (A) Prove the primary reference contains an “enabled disclosure;”
- (B) Explain the meaning of a term used in the primary reference; or
- (C) Show that a characteristic not disclosed in the reference is inherent.

10 MPEP § 2131.01.

Geng discloses that in a Matrigel assay, recombinant human Slit2 facilitated the in vitro neovasculature formation of HUVECs (Abstract 6.22). Human endothelial cells express Robo4 (Huminiecki, page 549, paragraph bridging left and right columns, page 550, left column, full paragraph 1 and page 551, Table 2). HUVECs are human endothelial cells. Therefore, Geng
15 discloses a method comprising activating Robo-4 receptor in endothelium tissue expressing Robo-4 receptor, wherein activating said Robo-4 receptor comprises providing a ligand of said Robo-4 receptor and allowing the ligand to bind to said Robo-4 receptor, wherein the ligand comprises Slit ligand, wherein the ligand comprises human Slit2 ligand.

“[P]reventing angiogenesis” is an intended use of the claimed method and does not
20 patentably distinguish the claimed method from Geng’s method.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7–12 and 19–22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the migration of HMVECs, does not reasonably provide enablement for directing the navigation of physiological tubular structures toward or away from a target tissue or for a method of preventing angiogenesis. The 5 specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are directed to or encompass a method directing the navigation of physiological tubular structures toward (claims 10–12) or away from (claims 7–9) a target tissue or a method of preventing angiogenesis (claims 19–22), comprising activating a Robo-4 receptor 10 with a ligand.

I. The following references provide evidence that contravenes the claimed outcome:

(1) Suchting (FASEB J. 2005 Jan;19(1):121-3) used the soluble extracellular domain of Robo4 as a probe of function in angiogenesis and endothelial biology. The soluble extracellular domain of the receptor (Robo4Fc) showed diverse in vivo and in vitro activities 15 including 1) inhibition of angiogenesis in vivo in the rodent subcutaneous sponge model, 2) inhibition of tube formation in the rat aortic ring assay, 3) inhibition of VEGF- and bFGF- stimulated endothelial cell migration, and 4) inhibition of endothelial proliferation. See the Abstract.

(2) Wang investigated whether Slit2 could regulate the migration of endothelial cells. 20 Similar to bFGF, purified recombinant human Slit2 protein induced the migration of HUVECs in a dose-dependent manner. See page 21, left column, full paragraph 1. Slit2 increased the generation of tubular networks of HUVECs in a dose-dependent manner, which indicated that

Slit2 has an angiogenic activity in vitro (page 21, right column, full paragraph 1). Slit2 overexpression increased microvessel densities (paragraph bridging pages 21-22 through page 22, paragraph bridging left and right columns).

(3) Bedell (Proc Natl Acad Sci U S A. 2005 May 3;102(18):6373-8) demonstrates

5 that roundabout4 signaling is essential for angiogenesis in vivo (page 6373, paragraph bridging left and right columns)

(4) Geng (FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A8) discloses that in a

Matrigel assay, recombinant human Slit2 facilitated the in vitro neovasculature formation of

HUVECs (Abstract 6.22). Geng also discloses that HEK293 cells secreting recombinant hSlit2

10 caused massive neovascular angiogenesis in the corneas of rabbits.

(5) Kaur discloses that vertebrates have evolved mechanisms that shut down guidance

signals in the absence of guidance molecules like robos, by simply collapsing the endothelial tip

in the case of vascular guidance. See Kaur (J Biol Chem. 2006 Apr 21;281(16):11347-56), page

11356, left column, last full paragraph.

15 II. The following references provide evidence that there is a lack of predictability in
the art:

(6) The role of the Slit family and their Robo receptors in vascular guidance thus

remains to be clarified. See Eichmann (Genes & Dev., May 1, 2005; 19(9): 1013 - 1021),

paragraph bridging pages 1015-1016 through page 1016, right column, full paragraph 1.

20 (7) Whether Robos mediate attraction or repulsion cues in terms of endothelial
guidance has remained controversial Our study reports a pathway that can be explained by
both attraction and repulsion mechanisms and suggests, perhaps, that this pathway may be

dynamically utilized to relay both signals arising from different ligands. See Kaur (J Biol Chem. 2006 Apr 21;281(16):11347-56), page 11355, left column, full paragraph 1.

Vascular guidance involves integrating multiple signaling cues both positive and negative to direct the endothelial tip through complex environment. Based on results here, we suggest

5 Robo4 functions as a one of the molecular rheostats in endothelial cells that regulate critical signals for steering the cell to its appropriate target. Because the decisions to move away or toward a target have to be made temporally and spatially in a rapid fashion, the robos have evolved an exquisite cross-talk mechanism ..., which results in an active competition for these proteins resulting in triggering attraction or repulsion mechanisms depending on cues from

10 surrounding milieu. Our study extends the current understanding of robo guidance mechanisms by including attraction to repulsion mechanisms and suggests that vertebrates have evolved mechanisms that shut down guidance signals in the absence of guidance molecules like robos, by simply collapsing the growth cone for axon guidance or endothelial tip in the case of vascular guidance. Identifying the GEFs or GAPs involved specifically in Robo4 signaling and

15 downstream players that induce Cdc42 and Rac1 signaling is a future goal that will shed light on how Robo4 mediates vascular guidance. See Kaur (J Biol Chem. 2006 Apr 21;281(16):11347-56), page 11356, left column, last full paragraph.

(8) Zhu (Neuron. 1999 Jul;23(3):473-85) used the aorta ring assay to investigate whether Slit repels endothelial cells (Malinda et al., 1999). It was found that Slit did not repel or

20 attract cells migrating out of the aorta (Figure 3F). When an endothelial cell line was tested, Slit also could not affect the direction of cell migration (data not shown). See paragraph bridging pages 475-476.

III. The following reference provides evidence that angiogenesis is complex:

(9) The regulatory systems involved in vascular formation are complex. See Fujiwara (Vasc Med. 2006 May;11(2):115-21), page 115, paragraph bridging left and right columns.

5 IV. The following reference provides evidence that vascular guidance is complex:

(10) Vascular guidance involves integrating multiple signaling cues both positive and negative to direct the endothelial tip through complex environment. Based on results here, we suggest Robo4 functions as a one of the molecular rheostats in endothelial cells that regulate critical signals for steering the cell to its appropriate target. Because the decisions to move away 10 or toward a target have to be made temporally and spatially in a rapid fashion, the robos have evolved an exquisite cross-talk mechanism ..., which results in an active competition for these proteins resulting in triggering attraction or repulsion mechanisms depending on cues from surrounding milieu. See Kaur (J Biol Chem. 2006 Apr 21;281(16):11347-56), page 11356, left column, last full paragraph.

15 V. The working examples and guidance in the specification are limited because:

(1) The one working example in the specification is limited to disclosing that Slit2 inhibits the migration of HMVECs expressing Robo4 (paragraph [0045]). However, Kaur provides evidence that Robo4 can trigger either attraction or repulsion mechanisms depending on cues from surrounding milieu, as discussed above.

20 (2) The specification provides prophetic examples of directing the navigation of

physiological tubular structures toward (paragraph [0047]) or away from (paragraph [0048]) a

target tissue and inhibiting angiogenesis (paragraph [0049]). There are no working examples wherein angiogenesis is prevented.

(3) In view of the contravening evidence and complexity in the art, the specification lacks guidance for preventing angiogenesis and directing the navigation of physiological tubular structures toward or away from a target tissue. For the specification to enable the skill artisan to make and use the claimed method it is incumbent upon applicant to set forth the procedures to achieve the desired results. Otherwise, the claims are an invitation to experiment.

VI. Claim 19 is directed to or encompasses a method of activating a Robo-4 receptor, which is analogous to a single means type of claim disparaged by the courts. A single means claim, i.e., where a means recitation does not appear in combination with another recited element of means, is subject to an undue breadth rejection under 35 U.S.C. 112, first paragraph. In re Hyatt, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983) (A single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification disclosed at most only those means known to the inventor.).

15 When claims depend on a recited property, a fact situation comparable to Hyatt is possible, where the claim covers every conceivable structure (means) for achieving the stated property (result) while the specification discloses at most only those known to the inventor.

VII. Claims 8, 11 and 21 are directed to a method utilizing any Slit ligand. Claim 22 is directed to a method utilizing a human Slit2 ligand. Suchting (FASEB J. 2005 Jan;19(1):121-3, 20 published online October 14, 2004, pages 1-17) sought to establish whether Robo4 functioned as a Slit receptor. Suchting was unable to demonstrate interaction between any known Slit protein and Robo4 but readily did so with Robo1. See paragraph bridging pages 6-7. Accordingly, there

is a lack of predictability in the art with respect to any Slit ligand or Slit2 ligand binding to and/or activation of Robo-4 receptor.

VIII. Claim 22 is directed to or encompasses a method directing the navigation of physiological tubular structures toward or away from a target tissue or a method of preventing angiogenesis utilizing a fragment of human Slit2 ligand. However, according to Nguyen (J Neurosci. 2001 Jun 15;21(12):4281-9), different axons have distinct responses to Slit2 fragments, and these proteins have different growth-promoting capacities (Abstract).

In terms of behavior, it has been long known that both nerves and blood vessels often follow similar routes and modes of migration during embryogenesis. In terms of molecules, observations in mouse and zebrafish have provided increasing evidence that the creation of 'higher order' blood vessel architecture is, partly, determined by families of proteins and signaling relays which have first been described in the developing nervous system. See Shima (Curr Opin Genet Dev. 2000 Oct;10(5):536-42), paragraph bridging pages 536-537.

Accordingly, there is a lack of predictability in the art with respect to navigation of physiological tubular structures toward or away from a target tissue or a method of preventing angiogenesis utilizing a fragment of human Slit2.

IX. Claims 7, 8, 10, 11 and 22 are directed to a method of directing the navigation of any physiological tracking tubular structure that expresses Robo-4 receptor. However, robos can trigger attraction or repulsion mechanisms depending on cues from surrounding milieu. See Kaur (J Biol Chem. 2006 Apr 21;281(16):11347-56), page 11356, left column, last full paragraph. Thus, how robos affect guidance is context dependent and there is a lack of predictability in the art.

In view of the breadth of the claims, the limited amount of direction and working examples provided by the inventor, the complexity and the unpredictability in the art and the quantity of experimentation needed to make or use the invention based on the content of the disclosure, it would require undue experimentation for the skilled artisan to make and/or use the 5 full scope of the claimed invention.

Claims 7, 9, 10, 12 and 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the 10 relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 7, 9, 10, 12 and 20 are directed to or encompass a method utilizing a ligand of a Robo-4 receptor. However, there is no structure associated with the “ligand of ...Robo-4 receptor” in the claimed method.

15 Regarding a Robo-4 receptor ligand and activating a Robo-4 receptor, the specification discloses the following:

20 [0052]Angiogenesis may be inhibited and/or prevented generally, without a directional limitation, in endothelium by activating Robo-4 receptor in the tissue. Activation of the receptor can be accomplished by any suitable technique, such as by providing a ligand of the Robo-4 receptor to the receptor, and allowing the ligand to bind to the receptor. Slit ligand is a particularly preferred ligand. The ligand can be provided in any suitable manner, such as by providing a soluble form of the receptor directly to the endothelium, by expressing the ligand in cells of the endothelium or adjacent tissue, or other suitable techniques. Also, fragments of 25 ligands of the Robo-4 receptor may be used. The fragment need only retain the ability to bind and activate the receptor. Also, activation of the Robo-4 receptor can be accomplished by other suitable techniques, such as by using agonosits of

the Robo-4 receptor, including monoclonal and polyclonal antibodies that bind and activate the receptor.

Neither the specification nor the claims limit the Robo-4 receptor ligand's structure.

5 Therefore, the Robo-4 receptor ligand is defined by function alone. That is not sufficient to satisfy the written description requirement. See Eli Lilly, 119 F.3d at 1568, 43 USPQ2d at 1406 ("definition by function ... does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is"). Therefore, applicants were not in possession of the Robo-4 receptor ligand genus.

10

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15 Claims 10–12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are directed to or encompass "a second cell mass," which implies or encompasses "a first cell mass." The metes and mounds of "a first cell mass" are not clearly set forth.

20 Claims 7–12 and 19–22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

25 The claims are directed to or encompass a Robo-4 receptor. According to the specification,

5 [0034] The invention also includes derivative, analog, and homolog polypeptides of those listed herein as SEQ ID NOS 3, 4, 5, and 6. As used herein, the terms derivative amino acid sequence, analog amino acid sequence, and homolog amino acid sequence have the same meaning as for the nucleic acid terms, described above, applied to polypeptides.

The specification describes derivative, analog and homolog nucleic acid sequences as follows:

10 [0029] The invention also includes derivative, analog, and homolog nucleic acid molecules of the polynucleotides of the invention, including the polynucleotides listed herein as SEQ ID 1 and SEQ ID 2. As used herein, the term "derivative nucleic acid molecule" refers to a nucleic acid sequences formed from native compounds either directly or by modification or partial substitution. As used herein, the term "analog nucleic acid molecule" refers to nucleic acid sequences that have a structure similar, but not identical, to the native compound but differ from it in respect to certain components or side chains. Analogs may be synthesized or from a different evolutionary origin. As used herein, the term "homolog nucleic acid molecule" refers to nucleic acid sequences of a particular gene that are derived from different species.

20 [0030] Derivatives and analogs may be full length or other than full length, if the derivative or analog contains a modified nucleic acid or amino acid. Derivatives or analogs of the polynucleotides of the invention include, but are not limited to, molecules comprising regions that are substantially homologous to the polynucleotides of the invention, including the polynucleotides listed herein as SEQ ID 1 and SEQ ID 2 by at least about 70%, 80%, or 95% identity over a nucleic acid of identical size or when compared to an aligned sequence in which the alignment is done by a homology algorithm, or whose encoding nucleic acid is capable of hybridizing to the complement of a sequence encoding a Robo-4 receptor.

25 [0031] "Homologous" nucleotide sequences encode those sequences coding for isoforms of the Robo-4 receptor. Homologous nucleotide sequences include nucleotide sequences encoding a polynucleotide for a Robo-4 receptor of species other than humans, such as vertebrates, e.g., frog, mouse, rat, rabbit, dog, cat, cow and horse. The polynucleotide listed herein as SEQ ID 1 is a cDNA sequence for the mouse Robo-4 receptor. Homologous nucleotide sequences also include naturally occurring allelic variations and mutations of the nucleotide sequences. A homologous nucleotide sequence does not, however, include the exact nucleotide sequence encoding the human Robo-4 receptor. Homologous nucleic acid sequences also include those nucleic acid sequences that encode conservative amino acid substitutions as well as a polypeptide possessing Robo-4 receptor

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biological activity. A conservative amino acid substitution is a change in the amino acid sequence that does not affect biological activity of the receptor.

5 [0032] In addition to the polynucleotide sequences shown in SEQ ID NOS 1 and 2, DNA sequence polymorphisms that change the amino acid sequences of the Robo-4 receptor may exist within a population. For example, allelic variation among individuals will exhibit genetic polymorphism in the Robo-4 receptor. As used herein, a "variant polynucleotide" is a nucleic acid molecule, or a complementary nucleic acid molecule, which encodes an active Robo-4 receptor that has at least about 80% nucleic acid sequence identity with a nucleic acid sequence encoding a full-length native Robo-4 receptor, or any other fragment of a full-length Robo-4 nucleic acid or complementary nucleic acid. Ordinarily, a variant polynucleotide will have at least about 80% nucleic acid sequence identity, more preferably at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 10 93%, 94%, 95%, 96%, 97%, 98% nucleic acid sequence identity and yet more preferably at least about 99% nucleic acid sequence identity with a nucleic acid sequence encoding a full-length native Robo-4 receptor, or complimentary nucleic acid molecule. Variant polynucleotides do not encompass the native nucleotide sequence.

15 20 Because the instant specification does not identify that material element or combination of elements which is unique to, and, therefore, definitive of "Robo-4 receptor" an artisan cannot determine what additional or material limitations are placed upon a claim by the presence of this element. The metes and bounds are not clearly set forth.

25 Conclusion

No claims are allowable.

30 ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (571) 272-0890. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 9:00 A.M. TO 5:30 P.M. IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, MANJUNATH RAO, CAN BE REACHED AT (571)272-0939.

35 30 IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE CENTRAL FAX NUMBER FOR OFFICIAL CORRESPONDENCE, WHICH IS (571) 273-8300.

CUSTOMERS ARE ALSO ADVISED TO USE CERTIFICATE OF FACSIMILE PROCEDURES WHEN SUBMITTING A REPLY TO A NON-FINAL OR FINAL OFFICE ACTION BY FACSIMILE (SEE 37 CFR 1.6 AND 1.8).

35 35 ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING MAY BE OBTAINED FROM THE PATENT APPLICATION INFORMATION RETRIEVAL (PAIR) SYSTEM. STATUS INFORMATION FOR PUBLISHED APPLICATIONS MAY BE OBTAINED FROM EITHER PRIVATE PAIR OR PUBLIC PAIR. STATUS INFORMATION FOR UNPUBLISHED APPLICATIONS IS AVAILABLE THROUGH PRIVATE PAIR ONLY. FOR MORE INFORMATION ABOUT THE PAIR SYSTEM, SEE [HTTP://PAIR-DIRECT.USPTO.GOV](http://PAIR-DIRECT.USPTO.GOV). CONTACT THE ELECTRONIC BUSINESS CENTER (EBC) AT 866-217-9197 (TOLL-FREE) FOR QUESTIONS ON ACCESS TO THE PRIVATE PAIR SYSTEM,

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DAVID ROMEO/

PRIMARY EXAMINER, ART UNIT 1647